

IDENTIFICATION AND DEVELOPMENT OF NEW CHEMICAL ENTITIES TO TREAT VISCERAL LEISHMANIASIS: A BUMPY ROAD

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All current treatments available for patients with visceral leishmaniasis have been developed several decades ago. Although numerous publications report the potential value of single molecules or chemical classes, not a single new chemical entity has been clinically evaluated. DNDi is trying to address this major need by gathering into a consortium the needed expertise to face this challenge. Two core organizations were selected, the Central Drug Research Institute (Lucknow, India) and Advinus Therapeutics (Bangalore, India). Various additional public or private partners are feeding this consortium with hit series. Since the inception of the program, six chemical series were investigated and currently three are undergoing thorough evaluation. One series, the 2-substituted quinolines, has been extensively studied with more than 450 molecules screened, 350 being synthesized *de novo*. Despite extensive work from medicinal chemistry to *in vivo* assessment through Drug Metabolism and Pharmacokinetics contribution, no molecule with the needed features to become a drug was identified. Iterative chemistry biology cycles allowed to significantly improve *in vitro* potency and selectivity as well as metabolic stability, but failed to produce a molecule with appropriate pharmacokinetic profile. Likewise, two other potentially interesting classes, buparvaquone and licochalcones A analogs, were investigated but did not provide promising leads. Recently, three new classes were made available to DNDi: the aminothiazides identified through the joint effort of DNDi with Institut Pasteur Korea; the oxaboroles from ANACOR pharmaceuticals; and the nitroimidazo-oxazoles/nitroimidazooxazines developed by the Global Alliance for Tuberculosis. Although none of these classes were originally developed against leishmaniasis, they have already produced advanced leads with robust features to become preclinical candidates. The work on these series illustrates the hurdles encountered to identify hits and to develop leads with the potential to become clinical candidates. It also stresses the strong need for new, well-characterized chemical series to compensate for expected attrition during later development stages.